Pancreatic Pathology

Introduction

This lesson is about the nonendocrine pancreatic pathologies—acute pancreatitis, chronic pancreatitis, and pancreatic cancer. Acute pancreatitis is the reversible inflammation of the exocrine parenchyma. The necrosis of the cells is permanent, but after a bout of acute pancreatitis, the organ can heal. Chronic pancreatitis is the irreversible destruction and subsequent fibrosis of the exocrine pancreas. A pancreas can regenerate from a bout of acute pancreatitis; chronic pancreatitis is scar and cannot regenerate. Chronic pancreatitis can be caused by acute pancreatitis or other mechanisms. Acute pancreatitis usually spares the endocrine function. Chronic pancreatitis, in severe forms, claims both exocrine and endocrine function. We'll spend a lot of time on pancreatitis, then spend the latter portion of the lesson on pancreatic cancer and the anatomic correlate, the Whipple procedure.

The endocrine pathologies of the pancreas—VIPoma (VIP), Zollinger-Ellison syndrome (gastrin), and diabetes mellitus (insulin)—are discussed elsewhere.

Acute Pancreatitis

Acute pancreatitis is caused by the premature activation of zymogens within the cells or ducts of the pancreas. Trypsinogen may spontaneously activate to trypsin. If that happens in the ducts of the pancreas, trypsin then does what it normally does in the duodenum—activate all the other zymogens. Trypsinogen is inactive and is supposed to be activated by the acidic environment of the proximal duodenum and the activating enzyme enteropeptidase (released by enterocytes of the proximal duodenum). Trypsin has reduced activity in the alkaline aqueous environment of the ducts of the pancreas (ductal cells secrete bicarbonate). Ductal secretions serve to flush the ducts of zymogen granules. Acinar cells also secrete trypsin inhibitors, which inactivate any trypsin that manages to get activated in the pancreatic ducts. With so many fail-safes, acute pancreatitis represents a catastrophic failure of the protective mechanisms.

	CAUSE	MECHANISM
I	Idiopathic	
G	Gallstones (second most common)	Choledocholithiasis, obstructs duct
E	EtOH (most common)	Direct toxin injury to acinar cells
T	Trauma (blunt force trauma as in MVA)	Direct injury to acinar cells
S	Shock	Ischemia kills
M	Mumps	
A	Autoimmune	IgG4 mediated, steroid-responsive chronic pancreatitis
S	Scorpion stings from Trinidad	
H	Hypertriglyceridemia	Familial causes with TG > 1000
E	ERPC	Iatrogenic, 30% of ERCPs cause pancreatitis
D	Drugs	HCTZ, TMP/SMX, "HAART", azathioprine, exenatide

Table 10.1: Causes of Acute Pancreatitis

Acute pancreatitis results in the autodigestion of the acinar cells by proteases and peripancreatic adipose by lipases. This leads to liquefactive necrosis of the pancreas and **fat necrosis** of the peripancreatic fat. It is the fat necrosis that predominates in the clinical evaluation of pancreatitis, as evidenced by the gross appearance, histological presentation of **saponification** (purple calcifications within adipocytes), and changes in labs, as we will discuss. The peripancreatic fat is abundant, and because the fat necrosis is so characteristic of pancreatitis, we say that pancreatitis presents as "fat necrosis." The acinar cells, not being adipose themselves, can obviously not undergo fat necrosis. And because the enzymes degrade the parenchyma of the pancreas into a soup, the necrosis must be liquefactive. But you cannot biopsy soup, so, if done, or if evaluated on autopsy, what is seen is the fat necrosis.

At least three distinct initiating events can cause the inappropriate activation of pancreatic enzymes, all of which are encompassed by the mnemonic, "I GET SMASHED." These three mechanisms are pancreatic duct obstruction, primary acinar injury, and impaired intracellular transport within the acinar cell. "I GET SMASHED" is intended to remind you that EtOH is the number one cause of acute pancreatitis, and leads to all three initiating events. Follow along with Figure 10.1.

Pancreatic duct obstruction. Obstruction of the pancreatic duct leads to the accumulation of pancreatic enzymes in the duct. Trypsinogen does undergo conversion to trypsin in the duct, but at a rate too slow to matter if there is flow. The alkaline environment and trypsin inhibitors prevent the activation of trypsin, but only temporarily, relying on the continuous production of bicarbonate and water to flush the duct free of activated enzymes. If obstructed, the flushing part of that protective mechanism cannot happen. Over time, more and more trypsin becomes activated. At a critical mass of activated trypsin, trypsin inhibitor is overwhelmed, and trypsin starts activating everything else. Obstruction of the pancreatic duct is caused by **gallstones** obstructing the hepatopancreatic ampulla. The presence of gallstones in the common bile duct is called choledocholithiasis. If the obstructing stone is below the pancreatic duct, it can cause gallstone pancreatitis. Chronic alcoholism can lead to a protein-rich secretion and the deposition of inspissated protein plugs, which increase the risk of obstruction without gallstones.

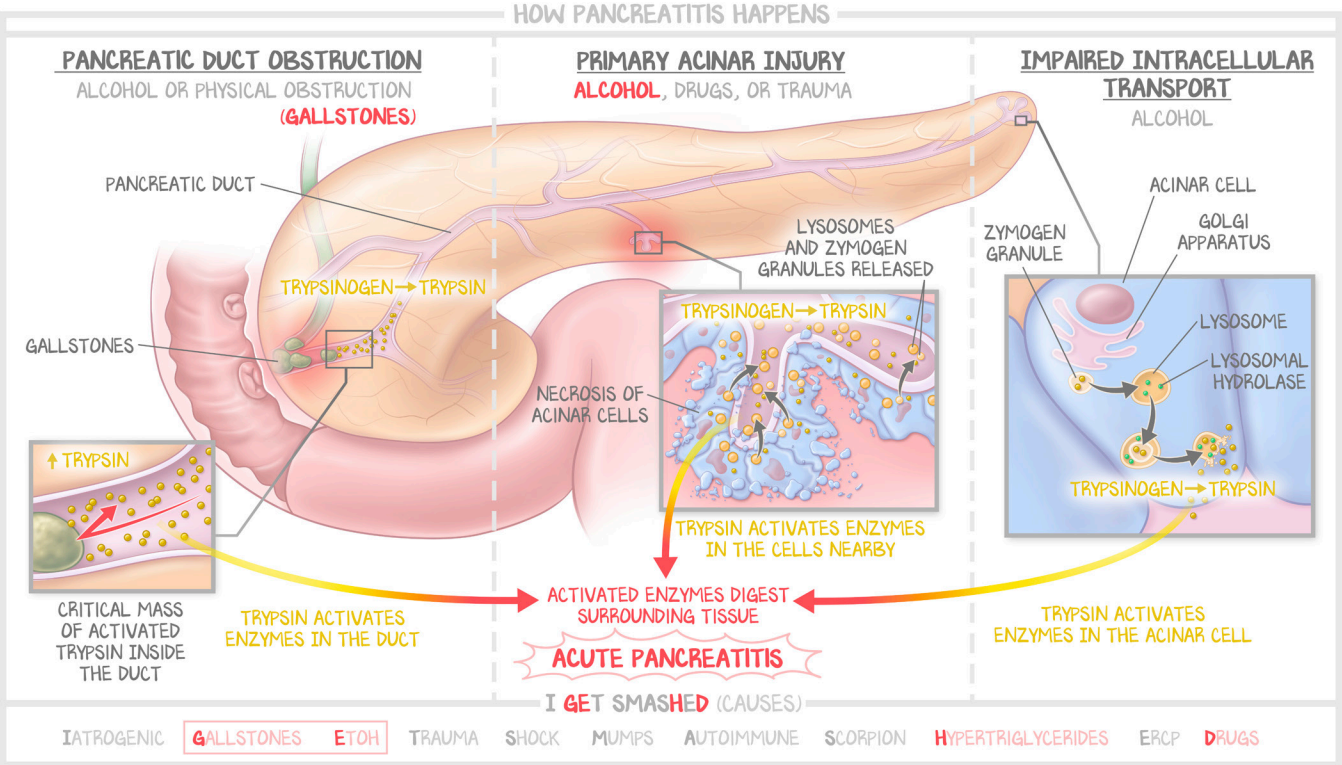

Figure 10.1: How Pancreatitis Happens

Acinar cell injury is a result of trauma (retrograde injection of dye in ERCP, a motor vehicle collision), ischemia (shock), or toxic exposure (alcohol, viruses, hypertriglyceridemia, drugs). Acinar cells undergo necrosis due to the initial insult. That necrosis causes the release of lysozymes and zymogen granules in the acinus. The individual cells become acidic (anaerobic metabolism causes pH to drop) as they necrose, and membrane permeability to calcium increases, both leading to the activation of the zymogens in the cells and the extracellular matrix the necrosis spills into. The death of a few acinar cells from the initial insult causes the release of enzymes that then begin the digestion of the rest of the pancreatic cells nearby.

Defective intracellular transport is a proposed mechanism only. Normally, lysosomal hydrolases and digestive enzymes are separated by the Golgi and are in distinct pathways. In acinar injury, if zymogens are delivered to lysosomal hydrolases, the zymogens would be activated.

Pancreatitis presents with **epigastric pain that radiates to the back**. Because of the embryologic origin of the pancreas, there is epigastric pain. Because it migrates to become secondarily retroperitoneal, it radiates to the back. Because secondarily retroperitoneal organs do have a layer of mesothelium (called the visceral peritoneum in the case of the pancreas), the pain is also **positional** (leaning back stretches the peritoneum, bringing the inflamed pancreas into contact with the peritoneum, whereas leaning forward relaxes the abdomen). Characteristic findings of **periumbilical ecchymosis** (Cullen's sign, "periumbilicullen's" sign) or **flank ecchymosis** (Grey Turner's sign, "*Turn on your side*" sign) are rare in acute presentations but classically present on licensing exams. **Anorexia** is a key feature to the diagnosis—not only do patients know it will hurt if they eat (because they already tried), but there will be no desire to eat. The diagnosis is made either with a **lipase** level three times the upper limit of normal or with **CT of the abdomen**. The lipase level is the preferred method of diagnosis, as CT should be reserved for later in the course to assess for complications or when the clinical suspicion of pancreatitis is high, but the laboratories are contradictory. Getting a CT at the time of diagnosis doesn't harm the patient, though it is radiation they didn't need. More importantly, an early CT affords false reassurance and can contribute to delay in obtaining a CT later when a complication develops. The use of amylase and lipase levels together has become routine practice. Amylase can be elevated due to vomiting without pancreatitis. Unless pancreatic-specific amylase levels are available, an amylase level is inferior to a lipase level and should not be used for diagnosis.

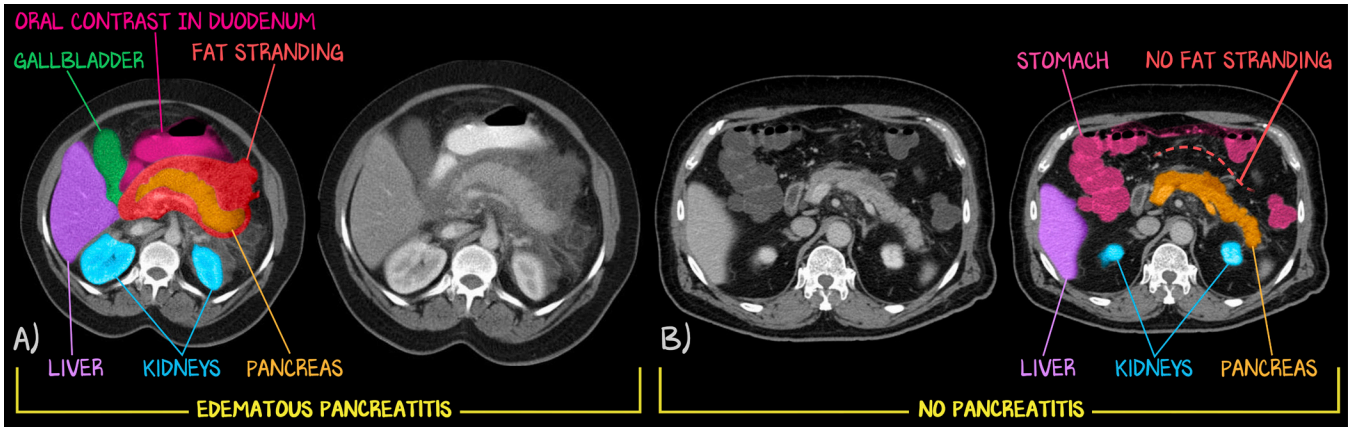

Figure 10.2: Acute Pancreatitis
(a) Axial CT demonstrating an edematous pancreas (the light grey swoop) with peripancreatic fat stranding (the darker grey schmooz around the light grey swoop). (B) Axial CT from the same patient 3 months later showing a normal pancreas with no edema and no peripancreatic fat.

Pancreatitis may present with a wide range of severity, from mild epigastric pain to full-blown septic shock with ARDS and DIC. The pancreas is intensely inflammatory, and with the release of proinflammatory cytokines, the patient may present as though they are septic, even though they are not infected. The **Ranson criteria**, as well as some other available scoring systems (APACHE-II), attempt

to predict mortality based on laboratories and clinical progression. Complications involve **hypocalcemia** due to fat saponification, **anemia** due to hemorrhagic pancreatitis, and **ARDS** due to volume overload—pancreatitis causes leaky capillaries, resulting in sequestration of fluid in the lungs despite the patient being intravascularly depleted. Therefore, these elements are included in the criteria to assess for prognosis. No system is useful for diagnosis, APACHE II is more complicated but more accurate, and the Ranson criteria are older but simpler. You should not memorize any prognostic calculator.

ADMISSION	AT 48 HOURS
Age > 55	HCt ↓ by 10% or more
WBC > 16,000	BUN increase > 5
LDH > 350	Serum calcium < 8
Glucose > 200	Arterial pO_2 < 60
AST > 250	Base deficit > 4
	Estimated fluid sequestration > 6 L

Table 10.2: Ranson Criteria

Older, sicker people with evidence of organ failure on admission are going to do worse. If there are signs of complications at 48 hours—ARDS, renal failure, hypocalcemia, anemia—they are going to do worse. Do not memorize this table. Pull it out when you see a patient with pancreatitis. Three signs carry a 20% mortality; 5 signs carry a 40% mortality.

Treatment is to **rest the bowel**. Any stimulation of the stomach or duodenum with water, food, or otherwise is going to stimulate the pancreas to secrete more zymogens. This will lead to further autodigestion. In the meantime, **analgesia** and **intravenous fluids** are the mainstays of support. Continuous infusion of an opioid (morphine, hydromorphone) at a low basal rate with patient-controlled, dose-and-time restricted boluses (lockout time is usually around 15 minutes) is superior to relying on nurse-administered, as-needed bolus dosing every 4–6 hours. If patients go without food for too long, parenteral (intravenous) nutrition can be provided. When they are ready to eat—when they want food—is the time to start advancing their diet. Early refeeding does not perform better than waiting for the patient to be ready.

There are three acute complications of acute pancreatitis—necrosis, hemorrhage, and abscess. **Necrotizing pancreatitis** shows evidence of necrosis on CT. These patients present as septic—fever, leukocytosis, tachycardia—which prompts the CT. Unless a sample of the necrosis reveals infection, antibiotics are not warranted. A sample of the necrotic tissue is obtained with a fine-needle aspiration. If the necrotizing pancreatitis is infected, choose **meropenem**. If ongoing necrosis occurs, a necrosectomy (surgical resection) may be necessary. **Abscess** formation requires drainage and intravenous antibiotics. **Hemorrhagic** pancreatitis requires blood products as necessary and monitoring for DIC.

There is one post-acute complication of acute pancreatitis—**pseudocyst**. It is not a cyst because it is not lined with epithelium. It is lined with **granulation tissue**. The inflammation around the pancreas is ongoing. Ongoing inflammation leads to macrophages clearing the "wound" and fibroblasts healing with granulation tissue. After the acute inflammation is over, the pseudocyst may persist. Those that are > 6 cm or that have been around > 6 weeks will need to be drained; those that are young or small may spontaneously resolve. The patient will present with **early satiety** (the cyst compressing the stomach). Large cysts may rupture, releasing digestive enzymes into the peritoneum, or they may become infected, resulting in an abscess.

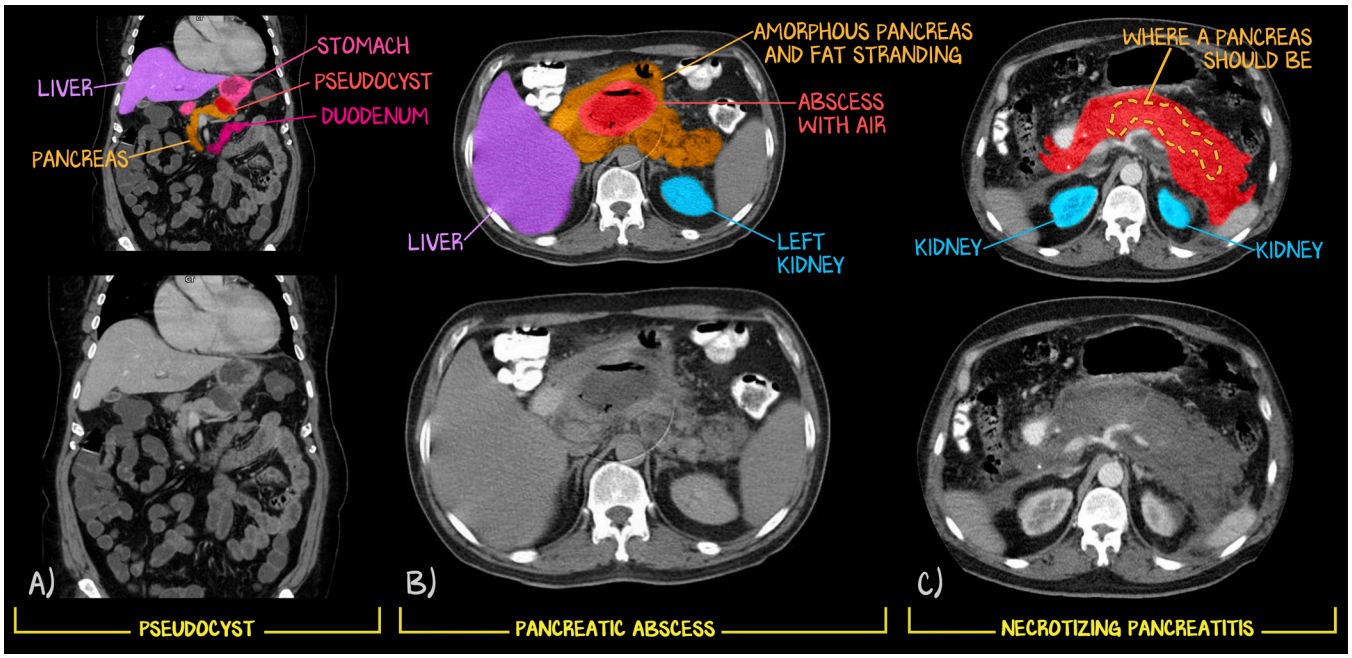

Figure 10.3: Radiographical Acute Pancreatitis Complications
(a) Coronal CT with intravenous contrast demonstrating a pseudocyst. A pseudocyst is a thinly lined collection of fluid, and the lining is only the granulation tissue. This pseudocyst is in the tail and abuts the stomach, inducing early satiety. (b) Axial CT with intravenous contrast demonstrating a pancreatic abscess. There is a walled-off collection of with gas bubbles where the neck of the pancreas should be. (c) Axial CT with intravenous contrast (the vessels light up bright) demonstrating near total necrosis of the pancreas. The amorphous grey blob should have contrast enhancement (where the pancreas is, the contrast goes), but this shows no contrast enhancement in the grey blob, indicating near-total necrosis.

There is one chronic complication of acute pancreatitis, especially with repeated bouts: **chronic pancreatitis**.

Chronic Pancreatitis

Chronic pancreatitis is not the premature activation of zymogens. If there is any remaining exocrine tissue, patients with chronic pancreatitis can have episodes of premature zymogen activation, but that is acute pancreatitis in the setting of chronic pancreatitis. Chronic pancreatitis is a misnomer, as there is no active inflammation. Histologically, that means that chronic pancreatitis does not have inflammatory cells on a slide. Chronic inflammation leads to **atrophy** and **fibrosis** of the exocrine tissue, and in severe forms, can claim the endocrine tissue as well. You should think of this as end-stage pancreatic disease, similar to ESRD or cirrhosis. The pancreas cannot do what it is supposed to do— release digestive enzymes—because the parenchyma is fibrotic, replaced with collagenous scar.

The most common cause of chronic pancreatitis in adults is alcohol, which causes **recurring bouts of acute pancreatitis**. In kids, genetic defects, such as cystic fibrosis, predominate. Pancreatic exocrine insufficiency, chronic malabsorption, and diabetes mellitus can all lead to significant morbidity and contribute to mortality. The 20-year mortality is 50%. With the loss of pancreatic proteases, protein malabsorption can cause the failure of development in children and wasting in adults. With the loss of lipases, fat malabsorption causes steatorrhea and fat-soluble vitamin (ADEK) deficiencies. If the endocrine function is compromised, insulin-dependent diabetes develops. Finally, there is an increased risk of pancreatic carcinoma—inflammation begets cancer.

Because the pancreatic function is burned out, even in acute pancreatic episodes, amylase and lipase levels may not be elevated. **CT** will show **dystrophic calcifications**, and ERCP/MRCP imaging will show a "chain of lakes" pattern due to the stenotic pancreatic ducts (due to fibrosis) intermixed with dilated normal pancreatic ducts. CT is used to rule out acute pancreatitis or make the diagnosis of chronic pancreatitis. MRCP is used when evaluating for malignancy.

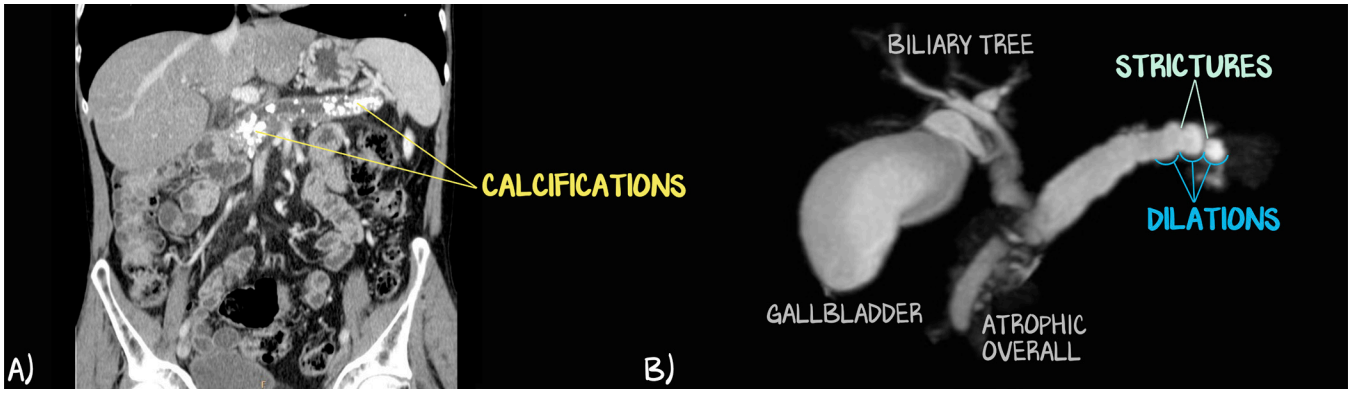

Figure 10.4: Imaging of Chronic Pancreatitis
(a) Abdominal CT demonstrates both calcification and atrophy of the pancreas, amongst other normal-appearing organs. The calcifications are most prominent in the tail and the neck, as indicated by the arrows. (b) Severe atrophy is noted, and the tail of the pancreas demonstrates strictures and dilations, the so-named "chains of lakes."

The patient will complain of the same pain as in acute pancreatitis. Resection does not help and only worsens endocrine function. Pain medication is required. **Enzyme replacement** is necessary for children with chronic pancreatitis to develop normally, and can be used in adults with evidence of malabsorption.

One distinct cause of chronic pancreatitis that needs to be separated from the others is **autoimmune pancreatitis**, caused by IgG4-secreting plasma cells. This form is important to recognize because it **will respond to steroids**. All other forms should be learned as unresponsive to treatment, with the only treatment being to replace what was lost—exocrine enzymes and insulin if necessary. Surgery does not improve pain but does worsen diabetes.

Pancreatic Cancer

When we say "pancreatic cancer," the disease we are referring to is **infiltrating intraductal adenocarcinoma**. It is the fourth leading cause of cancer deaths. It has one of the highest mortality rates of any cancer—five-year survival rate is less than 5%. This is because the pancreas is in the abdomen where its neck, body, and tail are essentially free-floating. There is no capsule or mesothelium to contain it, so it spreads locally, seeding the abdominal wall. By the time symptoms develop, the cancer has already progressed to an advanced stage. Cancers that form in the head of the pancreas can cause biliary duct obstruction and draw attention for painless jaundice. Those in the tail go silent until very late.

Pain is usually the first symptom, but by the time pain is felt, the cancer is beyond cure. **Obstructive jaundice** from cancer in the head of the pancreas rarely draws attention soon enough. Weight loss, anorexia, and malabsorption syndromes are signs of late disease. **Migratory thrombophlebitis** (named Trousseau's sign, after the physician who correctly self-diagnosed his own pancreatic cancer when he identified his own migratory thrombophlebitis) is superficial vessel inflammation due to the formation of clots that appear and disappear in various areas. This is a test favorite, but rare in patients with pancreatic cancer.

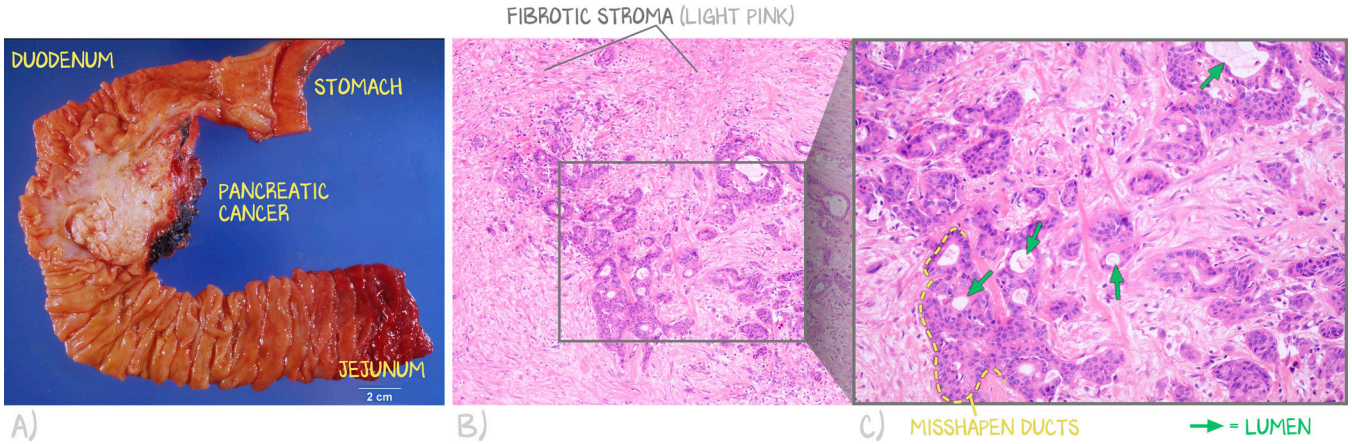

Figure 10.5: Adenocarcinoma of the Pancreas
(a) A specimen resected during a Whipple procedure for the treatment of pancreatic adenocarcinoma. In this image, the pylorus (distal part of the stomach) is seen at the top. The head of the pancreas is embedded within the "C" shape of the duodenum. The black color just to the right of the pancreas is ink that was applied by the pathologist just before they opened the specimen to take sections. It defines the surgical margin. (b) Intermediate-magnification view of moderately differentiated adenocarcinoma of the pancreas. The tumor is composed of distorted malignant glands that haphazardly infiltrate the stroma, which appears dense and fibrotic. Some of the glands contain intraluminal mucin. Many glands are poorly formed and have abortive or absent lumens. (c) High-magnification of the sample shown in panel b. The glands are of various size and shape. Some glands have lumens containing mucin. Most glands have abortive lumens or none at all. A few single tumor cells are seen infiltrating the stroma.

The normal pancreas progresses through a premalignant lesion called **pancreatic intraepithelial neoplasia** (PanIN). Genetic testing has recently developed an understanding of the progression of pancreatic cancer. ***KRAS*** is an oncogene that is most commonly associated with pancreatic cancer. It signals cell proliferation. *CDKN2A* is the most commonly inactivated tumor suppressor. *TP53* is also implicated. You will also see *KRAS* in colon cancers.

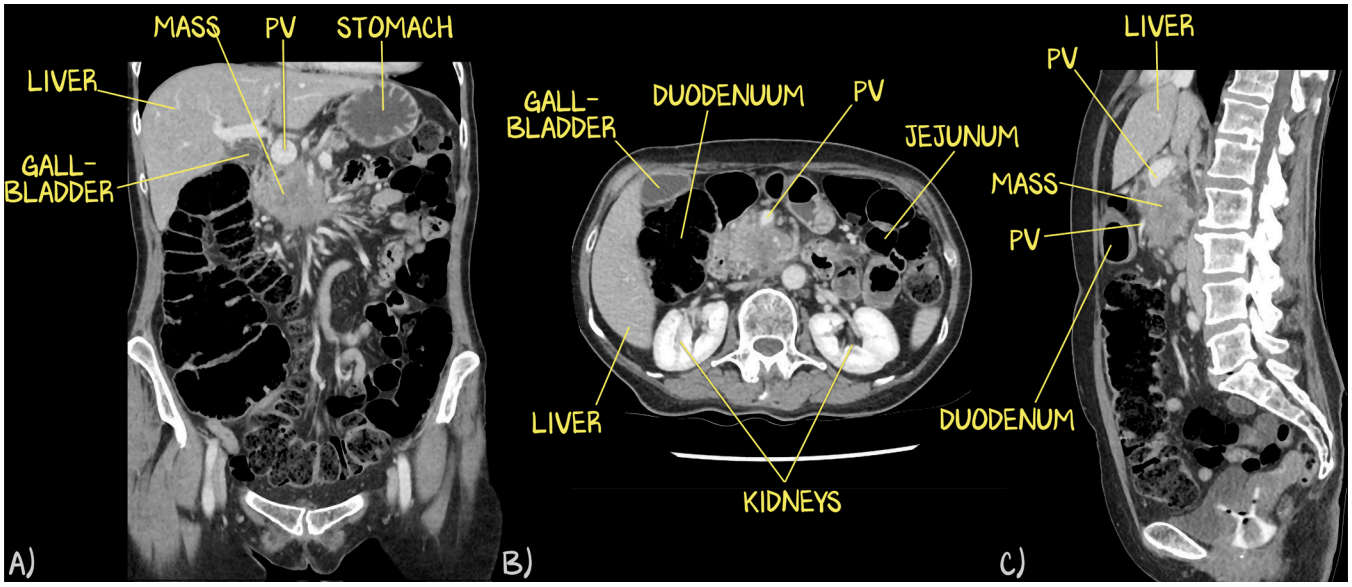

Figure 10.6: Adenocarcinoma of the Pancreas
(a) Abdominal CT, portal venous phase, coronal view. There is a large, hypodense mass arising from the pancreatic head that obscures the first portion of the duodenum. It completely encases the proximal portal vein (blue). Notice how all the splanchnic vessels are traveling into the mass, emerging above the mass as the portal vein. (b) Transverse section of the mass adjacent to the air-filled duodenum. (c) Sagittal section revealing just how big this mass is—it expands out in all directions, encasing the portal vein.

There is **no screening** test for pancreatic cancer. Most have invaded vessels, seeded other organs through the peritoneal cavity, or invaded structures that preclude the pancreas's removal. The head of the pancreas is near the SMA and SMV, as well as the IVC and aorta. **Smoking** and **chronic pancreatitis** are strong risk factors. *BRCA2* mutations and being of Ashkenazi descent increase risk. CA 19-9 and CEA protein levels can be used as serologic markers for recurrence or tracking the effect of treatment. They are not used for diagnosis.

Other Pancreatic Neoplasms

Serous cystic neoplasms are almost always benign and are associated with Von Hippel-Lindau syndrome. They are numerous and small. The cysts are lined with **cuboid** epithelium without atypia.

Mucinous cystic neoplasms occur in **women** and are a precursor to invasive mucinous adenocarcinoma. It is a painless, slow-growing mass. The cysts are huge and filled with mucin. Resection before malignant transformation (which also involves *KRAS* and p53 mutations) is curative. Most go unnoticed, and patients succumb to their disease because they arise in the **tail** of the pancreas. They consist of mucin-producing columnar epithelium with a dense stroma and thick mucin-filled cysts.

Intraductal papillary mucinous neoplasms (IPMN) occur in **men** and tend to **invade large ducts**. They tend to involve the **head** of the pancreas. They have papillary projections that fill the ducts. Resection is curative. Because they involve the head of the pancreas, these can produce symptoms early enough to catch. Malignant transformation involves *KRAS* and p53.

The Whipple Procedure

A **pancreaticoduodenectomy** (pancreas and duodenum resection) is the Whipple procedure. The goal is to remove the pancreatic head and the things that it could invade. The pancreas comes out to get the cancer. The duodenum is nestled right up against the pancreas, and it **shares the same blood supply**, so it comes out. The gallbladder and the biliary tree near the duodenum have a high risk of being invaded, so it is removed. The antrum of the stomach **shares the blood supply** of the head of the pancreas, so it is also removed. The remaining structures are reconnected. A loop of jejunum is brought up to the right upper quadrant. The hepatic bile duct (above the cystic duct) is connected to the remaining small bowel. The remaining pancreas is connected to the proximal small bowel. And the stomach, without a pylorus, is attached distally to the small bowel.

Immediately after surgery, the complications come from the anastomoses. Delayed gastric emptying due to stomach surgery is defined as the need for an NG tube for longer than 10 days. It has to do with the stunning of the stomach. The traditional Whipple procedure resects the pylorus, so it could not restrict any of the peristaltic contraction of the stomach, leaving the cause of delayed gastric emptying to be a problem with peristalsis. **Bile leak** may occur from the choledochojejunal anastomosis, and **pancreatic enzyme leak** may occur from the pancreatojejunal anastomosis.

The cancer is removed, but the ability to digest food is obviously overtly compromised. No pylorus or antrum for grinding. No proximal duodenum to signal the exocrine pancreas and bile release. Remnants of the organs are present, but the function is grossly compromised. Malabsorption syndrome is abundant, and pancreatic enzymes must be administered with each feeding. Vitamin supplementation is also required. Diabetes may result from the removal of endocrine tissue. For those who survive the Whipple, which are few, the quality of life is similar to those patients who have a laparoscopic cholecystectomy. The hard parts are getting diagnosed early enough to not have metastasis, suffer metastasis, and survive the procedure.

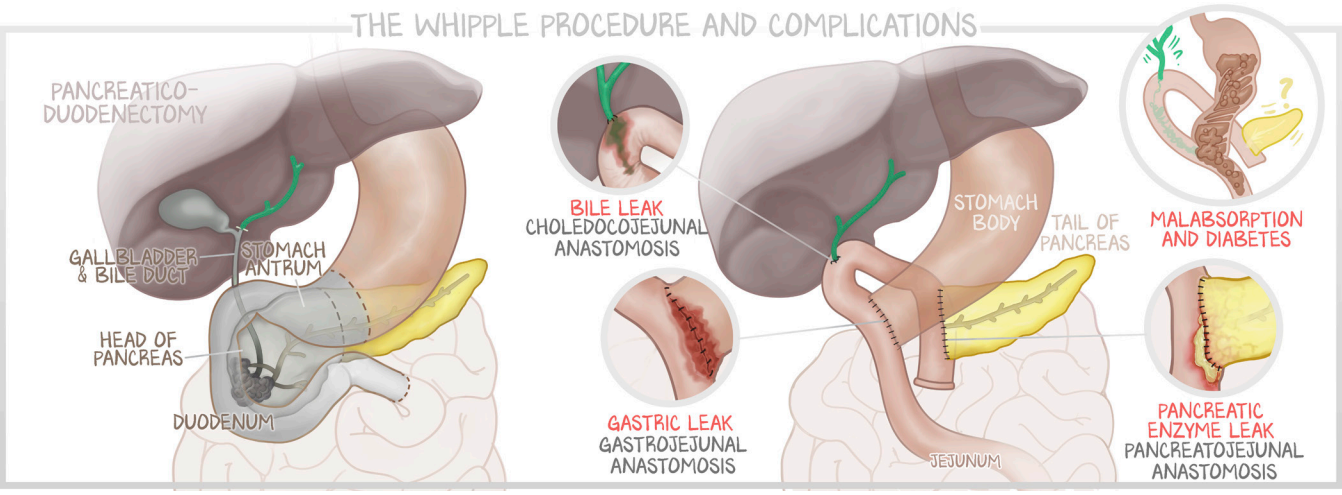

Figure 10.7: Whipple Procedure and Complications
A visualization of the Whipple procedure and its potential negative consequences.

Citations

Figures 10.2a, 10.2b, 10.3a, 10.3b, 10.6a, 10.6b, 10.6c: Courtesy of Radiopaedia.

Figures 10.5a, 10.5b, 10.5c: Courtesy of Webpathology.